PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of:

Darci T. HORNE *et al.*

Application No.: 09/880,107

Filed: June 14, 2001

For: GENE EXPRESSION PROFILES IN LIVER CANCER

Group Art Unit: 1634

Examiner: Chakrabarti, A. K.

Commissioner for Patents
Washington, D.C. 20231

Sir:

AMENDMENT

IN THE CLAIMS:

Please cancel non-elected claims 4, 8, 12 and 14-46 without prejudice or Applicants' disclaimer of the subject matter thereof. Applicants reserve the right to pursue the subject matter of the non-elected claims in a subsequent, divisional or continuing application.

Please add the following new claims 47-57:

47. A method of claim 1, wherein the level of expression of 5 or more genes from Tables 3-9 is detected.

48. A method of claim 1, wherein the level of expression of 10 or more genes from Tables 3-9 is detected.

49. A method of claim 1, wherein the level of expression of 100 or more genes from Tables 3-9 is detected.

50. A method of claim 1, wherein the level of expression is compared to the gene information in Tables 3-9.

51. A method of diagnosing liver cancer in a patient comprising:

(a) preparing a gene expression profile from a tissue sample; and

(b) comparing the gene expression profile to a database comprising part of the data in Tables 3-9.

52. A method of claim 51, wherein the cancer is hepatocellular carcinoma.

53. A method of claim 51, wherein the cancer is metastatic lung cancer.

54. A method of claim 51, wherein the database comprises substantially all of the data from Tables 3-9.

55. A method of claim 51, wherein the database comprises all of the data from Tables 3-9.

56. A method of claim 51, wherein the database comprises gene expression information for substantially all of the genes from Tables 3-9.

57. A method of claim 51, wherein the database comprises gene expression information for all of the genes from Tables 3-9.

REMARKS

Applicants respectfully submit that no prohibited new matter has been introduced by the foregoing amendment. All of new claims 47-57 are drawn to the same invention as the invention of Group I , which is the Group currently under consideration by the Examiner. Support for the new claims can be found throughout the specification as originally filed, for example at page 9, lines 9-15; and page 18, line 5 through page 20, line 30. It is understood that the additional number of species recited by the dependent claims 47-49 are entitled to consideration upon the allowance of the generic base claim (MPEP 809.02(a)).

The Office Action dated September 5, 2002 has been carefully reviewed and the following response is made in response thereto. In view of the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

I. Summary of the Office Action

1. Claims 1-3, 5-7, 9-11 and 13 were examined in the Office Action. Claims 4, 8, 12 and 14-46 were withdrawn by the Examiner.

2. The Office Action rejected claims 3 and 7 under 35 U.S.C. § 102(b) as being anticipated by Ohmachi *et al.*

4. The Office Action rejected claims 1, 2, 5 and 6 under 35 U.S.C. § 103 as being unpatentable over Ohmachi *et al.* in view of Hillier *et al.* and further in view of Tomita *et al.*

5. The Office Action rejected claims 9-11 and 13 under 35 U.S.C. § 103 as being unpatentable over Ohmachi *et al.* in view of Tomita *et al.*, further in view of Hillier *et al.* and further in view of Yeatman *et al.*

II. Response to the Office Action

Rejection of claims 3 and 7 under 35 U.S.C. § 102(b) as being anticipated by Ohmachi *et al.*

The Office Action alleges that the Ohmachi reference teaches monitoring the treatment of a patient with liver cancer or hepatocellular carcinoma (HCC). Applicants respectfully disagree with this position. Ohmachi teaches the expression of pancreatic secretory trypsin inhibitor (PSTI) gene in the liver of subjects infected with the hepatitis B virus (HBV) and correlates expression of the PSTI gene in HCC subjects and non-HCC subjects with HBV infection. The reference does not disclose the testing for PSTI gene expression for monitoring

the treatment of a patient with liver cancer or HCC. The Office Action contends that Table 1 and Figures 1 & 2 of the Ohmachi reference demonstrate the construction of a gene expression profile comparing PSTI expression of HCC subjects to normal controls. However, Table 1 merely shows that PSTI expression (last column of table) is closely correlated with HBV infection (columns 5-8 of table), rather than to HCC affliction of the subject (column 4 of table). In regard to Figure 1, what is depicted is the examination of 25 non-malignant liver tissues including 20 with chronic hepatitis and cirrhosis (page 1014, last 5 lines of column 1), not a comparison of normal versus HCC. Indeed, this is further confirmed by Ohmachi in the paragraph bridging the columns on page 1014, concluding with the statement, "[t]hese results indicate that neither chronic liver inflammation nor grade of hepatitis and cirrhosis were related to PSTI expression, and that only HBV infection was significantly associated with PSTI expression in liver tissues" (emphasis added for clarity).

In regard to Figure 2, what is depicted is a comparison of PSTI gene expression in cells co-transfected with HBV DNA or the HBV X protein versus cells co-transfected with a non-competent vector. This is an *in vitro* expression assay and is not equivalent to treating a subject with a pharmaceutical composition as alleged on page 3 of the Office Action. Further, the *in vitro* assay provides no correlation whatsoever to liver cancer or HCC or their comparison to normal tissues.

In view of the fact that the Ohmachi reference does not teach a correlation of the expression of any gene to monitoring the treatment of a liver cancer or HCC patient, the reference cannot be considered to anticipate the claimed invention, as it does not teach each and every element of the claim as required by the statue. Accordingly, Applicants respectfully request withdrawal of the ground of rejection.

Rejection of claims 1, 2, 5 and 6 under 35 U.S.C. § 103 as being unpatentable over Ohmachi *et al.* in view of Hillier *et al.* and further in view of Tomita *et al.*

The Office Action acknowledges that Ohmachi does not teach the liver genes having SEQ ID NOs: 2492 and 3847. However, the Office Action contends that the claimed invention would be obvious over Ohmachi when combined with the disclosure of the 2492 sequence by Hillier and of the 3487 sequence by Tomita. The Office Action alleges that it would be obvious to look for the GenBank sequence disclosed by Hillier because, according to the Office Action, Ohmachi notes that, "detecting any changes that occur in cellular gene expression including PSTI which are reproducibly augmented in HCCs and can naturally be used as a marker of diagnosis of

HCC." The Office Action further contends that the addition of the Tomita sequence would be obvious because Tomita discloses that PSTI is identical to growth factors isolated from hepatoma cells and because, according to the Office Action, Tomita notes that, "detecting any changes that occur in cellular gene expression including PSTI from human hepatoma cells and which can naturally be used as a marker of diagnosis of hepatoma."

Applicants respectfully traverse the ground of rejection. First, and incorporating the discussion *supra*, Ohmachi does not disclose a method for diagnosing (claims 1 & 5) or detecting the progression of (claims 2 & 6) liver cancer or HCC. What Ohmachi discloses is a correlation between PSTI expression and HBV infection and does not consider a diagnosis of any kind in relation to PSTI levels. Second, the Hillier reference is merely a GenBank entry recording the isolation of a nucleic acid sequence from spleen and liver tissue isolated from a 20 week-post conception fetus. Hillier does not assign any diagnostic value to the sequence, nor does Hillier provide any motivation whatsoever to search for the sequence in the investigation of adult human liver cancer. Third, Tomita in no way suggests the diagnosis of hepatoma by the presence of PSTI, rather Tomita discloses that this protein, a pancreatic enzyme, is produced by tumor cells from a number of tissues, rather than being indicative of any particular type of malignancy. In fact, Tomita did not even examine PSTI in hepatoma cells (see Table 1), but in the passage cited by the Office Action merely referred to another study where one of two endothelial growth factors isolated from hepatoma cells was identical to the 25 NH_2-terminal amino acids of PSTI. Further, Tomita does not assign any type of diagnostic relevance to PSTI expression.

Given the fact that Ohmachi does not disclose any type of method for diagnosing or detecting the progression of liver cancer or HCC and that neither Hillier nor Tomita corrects this deficiency, the present invention cannot be considered to be obvious over the combination of references. Accordingly, Applicants respectfully request withdrawal of the ground of rejection.

Rejection of claims 9-11 and 13 under 35 U.S.C. § 103 as being unpatentable over Ohmachi *et al.* in view of Tomita *et al.*, further in view of Hillier *et al.* and further in view of Yeatman *et al.*

The Office Action alleges that it would have been obvious to combine the teachings of Yeatman with those of Ohmachi, Hillier and Tomita because Yeatman was able to differentiate between "colon cancer cells that are highly-metastatic to the liver when compared with cells that are non-metastatic." Applicants respectfully traverse this ground of rejection. The claims at

hand are drawn to the diagnosis (claim 9), detecting the progression (claim 10) or monitoring the treatment (claim 11) of a metastatic liver cancer or differentiation between a metastatic liver cancer and HCC (claim 13). The Yeatman reference, in contrast, is directed to differentiating between colon cancer cells which are highly-metastatic to the liver and colon cancer cells that are non-metastatic to the liver. At no point does the Yeatman reference become concerned with HCC. Furthermore, there is no suggestion of comparing the differential expression of at least two genes found in Tables 3-9 of the instant specification, as required by claims 9, 10 and 13, only the expression of a single probe target in three cell lines.

Given these differences from the present invention and the fact that the Yeatman reference fails to make up for any of the deficiencies already noted for the Ohmachi, Hillier and Tomita references, the present invention cannot be considered to be obvious over the combination of these references. Accordingly, Applicants respectfully request withdrawal of the ground of rejection.

Conclusion.

In view of the foregoing remarks, the Applicants respectfully request withdrawal of all outstanding rejections and early notice of allowance to that effect.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

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